cell receptor, or an Fc receptor, and (c) an intracellular domain that does not signal target cell or target infective agent destruction; and

the second of said receptors comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective agent, and (b) an intracellular portion which is derived from CD28.

REMARKS

Claims 44-47, 51-52, 72-75, 79, and 100 are pending in this application. These claims stand rejected under 35 U.S.C. § 103. This rejection is addressed below.

Amendment

Claims 44 and 79 have been amended to more clearly define applicants' invention, which is a cell expressing a combination of two chimeric receptors; the first receptor includes an extracellular binding domain joined to a transmembrane domain that triggers an immune effector response in the absence of an intracellular signalling domain, and the second receptor includes an extracellular binding domain joined to a CD28 intracellular portion. This amendment, which specifies that the immune receptor transmembrane domain provides the signalling function to the first of the two chimeric receptors, finds support in the specification, for example, at page 48 and in Figures 8a and 8b.

Rejection under 35 U.S.C. § 103

Claims 44-47, 51-52, 72-75, 79, and 100 stand rejected, under 35 U.S.C. § 103, over a combination of Capon (U.S. Patent No. 5,359,046), Harding, Schwartz, and Romeo.[1] As applied to the presently amended claims, this rejection is respectfully traversed.

In general, applicants' invention features cells expressing a combination of immune cell chimeric receptors and CD28 chimeric receptors. The immune cell chimeric receptors signal target cell destruction through a transmembrane domain, rather than a cytoplasmic (intracellular) domain. Such receptors, working together with CD28 chimeric receptors, direct the recognition and destruction of specific targets, such as pathogens or cells infected with pathogenic agents such as HIV.

The cited references do not provide the combination of an immune cell receptor chimera that signals through a transmembrane domain and a CD28 chimera, or a cell expressing these chimeras which signals an immune effector response. Neither do these references provide any motivation for constructing a cell having such a pair of receptors.

Looking to these references, Capon never teaches or suggests the construction of

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[1] Applicants note that this rejection is based on the statement in the Office Action that "it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to be motivated to make a cytotoxic T lymphocyte with two chimeric receptors, both with CD4 as an extracellular domain, one with an intracellular zeta chain of a TCR and the other with a CD28 intracellular chain." In addressing this rejection, applicants have assumed that "intracellular zeta chain" was a typographical error and that "transmembrane zeta chain" was intended.

an immune receptor chimera having a transmembrane signalling domain. Nor does Capon suggest that an immune receptor transmembrane domain alone would be capable of signalling target cell destruction. In addition, Capon does not suggest or motivate the combination of any immune cell receptor chimera with a CD28 chimera, never in fact mentioning CD28 at all.

The secondary references, Harding and Schwartz, discuss the CD28 protein and its interaction with another protein, termed B7, but do not teach or suggest that the intracellular portion of CD28 should or could be used in a chimeric receptor with a heterologous, ligand-binding extracellular domain. Nor do Harding or Schwartz teach or suggest that CD28 chimeras should be used in conjunction with other chimeric receptors bearing a transmembrane domain from a T cell receptor, B cell receptor, or Fc receptor polypeptide.

And the final reference, Romeo, if anything, teaches away from the present invention because Romeo demonstrates that CD28 alone is not capable of signalling target cell destruction. Specifically, Romeo describes the construction of a CD28 chimera in which a CD28 cytoplasmic domain is fused to a CD7 transmembrane domain and a CD16 extracellular domain. In Figure 7 and at page 123, Romeo states that this CD28 chimera and, in particular, its cytoplasmic domain lacks cytolytic function. This fact would discourage one skilled in the art from using CD28 in the context of a chimeric immune receptor whose role is the signalling of cytolytic responses and would therefore

discourage the construction of applicants' dual receptor-expressing cells.

For all of the above reasons, applicants submit that the cited references do not provide a basis for either the prior art combination cited in the Office Action or the construction of applicants' dual chimeric receptor-containing cells. The § 103 rejection in this case may be withdrawn.

Conclusion

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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